Cognitive Enhancement
Practical & Ethical Considerations

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Learning Objectives

1. To be aware of the controversies surrounding “neuroenhancement”.
2. To review the efficacy and evidence of cognitive enhancement.
3. To address the ethical issues of cognitive enhancement using medications.
4. To be aware of the resources available for further learning.
Why a Public Discussion on Cognitive Enhancement

1. Have been prescribing ADHD medications for 30 years. We know these medications improve “normal” functioning.

2. There are ongoing controversies in the science and ethical journals.¹

3. Debate has not yet reached mainstream, clinical psychiatry – where the “rubber hits the road”

A New Cognitive Enhancer

- Antagonist of adenosine receptors
- Leads to increases in:
  1. Dopamine
  2. Acetylcholine
  3. Serotonin
  4. Glutamate
Positive Effects

1. Improves motor functioning during fatigued states.¹
2. Improves cognitive functioning.
3. Increased feelings of well being, relaxation, alertness and concentration.
4. Improved information processing and memory.
5. Neuroprotective effects from long-term use in both animal and human subjects.²
6. Increased muscarinic and nicotinic receptors in animal brain.

7. Lower incidence of Alzheimer’s Disease of between 30 – 60%.\textsuperscript{8}

8. Reduced risk of depression.\textsuperscript{3}

9. No negative health outcomes.

10. 100-mg. dose reduced omission errors, false alarms, reaction times and increased vigilance.\textsuperscript{4}
Positive Effects

11. Improves passing accuracy and jump performance in football (soccer).\textsuperscript{5}

12. Robust improvement on NART and WTAR in the elderly.\textsuperscript{6}

13. Improves brain functioning, by conditioning, even in the absence of the drug.\textsuperscript{7}
1. Should this medication be available for general use?

2. Who would be interested in participating in a clinical trial or trying this medication?
Caffeine

- Methylxanthine
- Antagonist of adenosine receptors
- Adenosine – ubiquitous nucloside that is a homostatic regulator
- Caffeine blocks $A_1$ receptors in brain that are inhibitory and $A_{2A}$ receptors in the basal ganglion that are excitatory.
References


Definitions

- Cogniceuticals (Russo 2007)
  - Pharmaceuticals that effect cognition
- Nootropics
  - Products including drugs, supplements and nutraceuticals that improve cognition, memory, intelligence and attention
- Nutraceuticals
  - A food or food product that provides health or medical benefits, example - brahmi
- Neuroenhancement
  - Prescribing medications to normal adults for purposes of augmenting their normal cognitive or affective function
Cognitive Enhancers
Cognitive Enhancement

- Enhancement increases an individual’s ability beyond normal
- Restoration returns diminished function to the normal range
Cognitive Enhancers
Cognitive Enhancers

PositScience®
Brain training software

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Think Faster
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Remember More

Which program is right for you?

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& Feel Sharper through auditory brain training.

Focus Better
& Feel More Alert.

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& Feel More Alert.

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Other Types of Cognitive Enhancers

1. Reading
2. Writing
3. Private Schools
4. Telescopes
5. Personal Computing Devices
6. ? Brain Chips
7. ? Brain Training
8. ? Transcranial direct current stimulation
9. ? Transcranial magnetic stimulation

3 Synder, A. Concept formation, *J. Integ Neuro Science*, 2004; 3(1) : Pp 31-46
Transcranial Direct Current Stimulation

- Weak current tDCS was applied to 15 healthy subjects
- Target – posterior perisylvian region (ppr)
- Included sham conditions
- Visual picture naming task was faster in all subjects following stimulation of the left ppr

Why Are People Interested In Cognitive Enhancement?

“Man is not going to wait passively for millions of years before evolution offers him a better brain.”

Cornelieu Giurgea
Romanian Neuroscientist 1960
Why Are People Interested In Cognitive Enhancement?

Aging

“Preservation of brain function into advanced age has not kept pace with the maintenance of peripheral organs”.¹

- Cognitive abilities decline with age
- Experiments with adults age 21 and age 72
  - Memory declines with age
  - Susceptibility to misinformation increases with age

- Cognitive speed
- Inhibitory function
- Memory
- Brain volume
- Brain activity
- Prefrontal white matter most susceptible

¹Saunders, J. The effects of age on remembering and knowing misinformation, Memory, 2010 18(1) Pp 1 – 11
²Ebmeier, K. Normal cognitive decline or dementia? The Practitioner 2010; 254: Pp 23-27
³Grady, C, Cognitive Neuroscience of Aging; Ann. N.Y. Acad. Sci. 2008; 1124 – Pp 127-144
AAMI Prevalence Estimated From Standard Clinical Memory Tests

AAMI = Age Associated Memory Impairment

Percent Meeting Objective AAMI Performance Criteria on Traditional Tests

Age Ranges

Crook, T.H. *The Memory Advantage* 2006; Figure 7 Pp 30
Why Are People Interested In Cognitive Enhancement?

Competitive Environment
We are in an environment that is becoming increasingly competitive cognitively.

- best university
- best job
- best lecture
- best research proposal

Success in life can depend upon superior cognitive functioning.
Methods of Enhancing Cognition

1. Mental exercises
2. Diet
3. Exercise
4. Medication
Training In Working Memory

Strategies
- elaborate encoding
- using mental stories
- imagery
- relationship between new and currently memorized material
- rehearsing out loud

Questions
1. Does this generalize to daily life?
2. How long do the effects last?

Effects of Diet and Exercise

Omega 3 fatty acids
Curcumin (tumeric)
Vigorous exercise

All increase brain-derived neurotropic factor (BDNF)

**BDNF**
- Modulates efficacy of synaptic transmission
- Stimulates synaptic and cognitive plasticity

Gomez-Pinilla, F. Collaborative effects of diet and exercise on cognitive enhancement, *Nutr Health* 2011: 20 (3-4), 165-169
Agents That Could Be Considered Cognitive Enhancers

1. Cholinergic Agents
2. Nicotine Agents
3. Glutamatergic Agents memory, attention
4. Stimulants (dopamine enhancers)$^1$
5. Mirtazapine attention

Public Demand

➢ Nutritional supplements that promise improved memory > $1B in the U.S.

$^1$Backman, L. Linking cognitive aging to dopamine; *Neurosci. Biobehav. Reviews* 2010; 34: Pp 670-677
Attention

ADHD or related medications

- Amphetamine
- Atomoxetine
- Methylphenidate
- Modafinil

- improve working memory, processing speed, declarative memory, executive memory, cognitive control
Current Use of Pharmaceutical Enhancers
Stimulant Use in U.S. Colleges

• Sample of 10,904 college students in 2001 self administered mail survey – response rate 52%

Results
• Non-medical stimulant use (Ritalin, Dexedrine, Adderall)
  • Life time 6.9%
  • Past year 4.1% in one site 25%
  • Past month 2.1%
  • White, male, lower grade point average
  • Highest rates
    1. North eastern U.S
    2. More competitive admission standards
  • More likely to use other substances
  • Obtained from peers and friends
Why Do Students Use ADHD Meds?

- Web Survey – 3,400 under graduate students
- 6 month prevalence of non medical ADHD use 5.4%
  1. Concentrate for studying 3.6
  2. Study longer 3.4
  3. Less restless when studying 2.8
  4. Concentrate in class 1.9
  5. Less restless in class 1.6
  6. Keep track of assignments 1.6
  7. Feel better 1.5
  8. Get high 1.4
  9. To prolong effects of alcohol 1.4
  10. Prevent other student from having an academic edge 1.3

- A positive screening for ADHD was associated with non medical use of stimulants in 12,000 Canadian students grade 7 – 12.

¹Rabiner, D, Motives and Perceived Consequences of Nonmedical ADHD Medication Use by College Students, J of Att. Disorders, 2009 Pp 259 – 270
²Poulin, C From attention-deficit/hyperactivity disorder to medical stimulant use to the diversion of prescribed stimulants to nonmedical stimulant use, Addiction, 2007; 102: Pp 740-751
Non Medical Use of Stimulants

National Survey on Drug Use and Health (2008)
Non-medical use of stimulants
- Life time prevalence > 12: 8.5%
- Ages 21 – 25: 12.3%

Obtaining Neuro Enhancers

All medications referenced in this workshop can be purchased online using credit cards, with no prescription or no medical examination! To Buy Adderall On Line, Click Here
Use By Scientists and Researchers

1. Internet poll from Nature¹
2. 1,400 scientists, 60 different countries
3. 20% had used cognitive enhancers
  ➢ 62% Methylphenidate
  ➢ 44% Modafinil
Why?
   a) Improve concentration
   b) For a specific task
   c) Jet lag
4. Recent meeting in Hong Kong – informal poll confirmed significant use in neuroscience researchers²

²Congress of Neuropsychopharmacology, 2010
Sleep Deprived Emergency Physicians

1. Double blind, random crossover
2. Modafinil improved:
   a. Sustained attention
   b. Cognitive control
   c. Working memory
   d. Self reported ability to attend lectures and learn
3. Equivocal results in non sleep deprived normals

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2 Randall, D, The cognitive enhancing properties of modafinil are limited in non sleep deprived middle-aged volunteers, *Pharmacology, Biochemistry and Behavior*, 2004 77 Pp 547-555
Review of Effectiveness

Medications for:
1. Alzheimer’s
2. ADHD
3. Narcolepsy

Cognitive enhancement in healthy subjects. Modest improvement in:
1. Working memory
2. Executive functions
3. Sustained attention
4. Episodic memory

de Jongh, R. Boxtox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories; *Neuroscience and Biobehavioral Reviews* 32 (2008) Pp 760-776
What Is Being Enhanced?

1. Memory
2. Attention
3. Creativity

Memory

- Neurogenesis can take place in hippocampus
- Drugs acting on neurotransmitters
  1. Acetylcholine
  2. Nicotine

Cognitive functions contributing to mental performance are distinct but heavily intermingled.
Ampakines

- Are not agonists or antagonist of neurotransmitters
- Modify receptor biophysics by modifying synaptic current
- Have shown interesting results in memory enhancement in “normal subjects”

Memory enhancement: the search for mechanism-based drugs

Effects of a positive modulator on the recall of nonsense syllables by aged subjects.

Four groups of healthy 65–75 year old subjects were given a list of 10 nonsense syllables and then asked to recall them without prompting 5 minutes later. Three of the groups were given the ampakine CX516 at the indicated dosages. Retention scores (mean ± s.e.m.) are shown; the differences were significant (ANOVA). Right, the drugs did not detectably affect heart rate; blood values in the low micromolar range were associated with improved memory scores

Ampakines

- Enhance attention, alertness, learning, memory
- Interest with glutamatergic AMPA receptors
- Being developed by Cortex, Shire, Servier
- One compound CX717 in Phase II trials
- Phase II completed March 3, 2008\(^1\)
- Ampalex CX516 – can be purchased on line from China

\(^1\)ClinicalTrials.gov
The Future

As of 2008, 32 compounds in clinical trials for treatment of cognitive impairment.

1. Acetylcholinesterase Inhibitors
2. Nicotinic Acetylcholine Receptor Agonists
3. Serotonin Receptor Antagonists
4. GABA Agonists
5. Multi Functional Drugs
   - Mostly targeted at Alzheimer’s
   - Current Alzheimer’s market $3.8 billion/year
   - These new compounds are the most likely candidates for cognitive enhancement.

Buccafusco, J. J. Emerging cognitive enhancing drugs; Expert Opinion 2009; 14: Pp 577-589
The Future

1. Purposeful development of drugs for enhancement of normal functioning – unlikely

2. Expansion of:
   a) Existing diseases to include “mild” states
   b) New disease entities, i.e. “shift worker syndrome”

3. More “off label” use – example 90% of prescriptions for Modafinil are “off label”¹

   - Manufacturer applied for a license for “profound sleepiness” but was approved for Obstructive Sleep Apnea and Shift Work Sleep Disorder

4. More development for disease specific states, dementia, ADHD etc.

¹Vastab, B. Wakefulness enhancer raises concerns; *JAMA* 2004 291: Pp 167-70
Ethics

A branch of philosophy that addresses questions about morality – that is, concepts such as good and bad.
Neuroethics

The examination of what is right and wrong, good and bad about the treatment of, perfection of or unwelcome invasion of and worrisome manipulation of the human brain

William Safire
Ethical Issues

1. Liberal viewpoint
   - Everyone should do what they want as long as it does not cause others harm
2. Distributive justice
   - Everyone should have equal access to beneficial treatments
   - Our society tolerates inequality of resources, e.g. private MRIs, cosmetic surgery, private schools
3. Moral framework for testing in “normal” subjects is not developed
4. Expansion of existing medical diagnoses and emergence of new categories
5. Coercion
   - Could individuals be forced by their employers, peers or other to take cognitive enhancers?
   - School attendance is current mandatory for children.
6. Use of language can define the debate
   - ? Prescription Drug Diversion\(^1\)
   - ? Prescription Drug Abuse
   - ? Cognitive Enhancement
   - ? Life Style Choice
7. A waste of scarce medical resources
   - Compare with plastic surgery
8. Treatment for unhealthy labor practices
   - Long hours
   - Shift work

\(^1\)Racine E., Cognitive Enhancement *Neuroethics* 2010 3: Pp 1-4
1. **Neuroethics Society**
   - To promote the development and responsible application of neuroscience through research, education and public engagement
   - Can join for $60/year
   - [www.neuroethicssociety.org](http://www.neuroethicssociety.org)

2. **Neuroethics (Journal)**
   - New journal with international focus
   - Published since 2008
   - [http://www.springer.com/content/120989/](http://www.springer.com/content/120989/)

Recent Article – Racine, E. Cognitive Enhancement, Lifestyle Choice or Misuse of Prescription Drugs, *Neuroethics* 2010 3 Pp 1-4
1. Prescription of medication for neuroenhancement is:
   - Not legally obligatory
   - Not legally prohibited
   - Legally permissible (in the U.S.)

2. Neuroenhancement would be prescribed for improving the wellbeing of the patient

3. “Off-label” use of medication

4. Very little in the way of valid studies on “normal” populations.
My (Tentative) Position

The Facts

1. Informed healthy adults are obtaining cognitive enhancers from:
   a) Internet
   b) Friends

2. The market for cognitive enhancement is expanding:
   a) Increased demands
   b) Graying population with intellectual decline
   c) Awareness in popular media

3. Doctors are increasingly skirting regulators thru “off label” prescribing
My (Tentative) Position

Healthy, informed adults seeking cognitive enhancers should have these medications prescribed by doctors:

Why?
1. Better regulation than informal market
2. Screening for health issues
3. Medical monitoring